Injured body, injured soul? Predicting and preventing posttraumatic stress disorder after injury
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Citation for published version (APA):
CHAPTER 8: Discussion
8.1 OVERVIEW OF THE THESIS

The findings presented in this thesis centred on the prediction and prevention of psychological symptoms, especially PTSD symptoms, as a consequence of traumatic injury. The aims of the studies were: (1) to investigate the predictive role of acute post-injury cortisol and DHEAS for acute and chronic PTSD (Chapter 2); (2) to examine the diagnostic accuracy of three early screening instruments for 6-month PTSD (Chapter 3); (3) to develop and test the effectiveness of a web-based early psychological intervention to prevent PTSD in injured trauma survivors (Chapters 4, 5, and 6); and (4) to investigate the association between early pharmacotherapy within the initial 48 hours of injury and PTSD at 6 weeks and within the first year after trauma (Chapter 7). In this general discussion, I will summarize the main findings of our research, discuss methodological considerations, and provide practical and clinical implications for the results of the studies.

8.2 CONCLUSIONS

8.2.1 Cortisol and DHEAS as predictors for PTSD (Chapter 2)

To examine whether acute plasma cortisol and DHEAS levels predict later PTSD, data from 397 adult injury patients from the AMC’s and VUmc’s Trauma Units were collected. The results showed that patients with lower acute cortisol levels to trauma were more likely to develop acute and chronic PTSD symptoms. These results were independent from known confounding factors, such as age, gender, time of blood sampling, injury severity, trauma history, and ICU admission. Higher acute DHEAS levels and a smaller cortisol-to-DHEAS ratio were found to contribute to 6-week PTSD symptoms, but not after controlling for the same confounding factors, and not at 6 months. Diagnoses of acute or chronic PTSD were not predicted by cortisol, DHEAS or cortisol-to-DHEAS ratio. Lastly, acute DHEAS did not contribute significantly to PTSD symptom change between 6 weeks and 6 months.

Our findings confirm the hypothesis that insufficient activation of the HPA-axis in response to stress may lead to the development of PTSD (Yehuda, 2002). More specifically, our results of low levels of circulating cortisol marking a vulnerability factor for developing PTSD symptoms are in line with several previous studies (Aardal-Eriksson et al., 2001; Delahanty et al., 2000; Ehring et al., 2008; McFarlane et al., 2011), but not with studies who found no association between cortisol and PTSD (Bonne et al., 2003; Resnick et al., 1997; Shalev et al., 2008). Our results also indicate that cortisol is not only a predictor for acute PTSD symptoms, but continues to predict chronic PTSD symptoms at 6 months, even when controlling for relevant trauma and injury characteristics. Regarding acute DHEAS, our study was the first prospective investigation of its role in the prediction of PTSD. It was concluded that
DHEAS responses differ between trauma-exposed individuals compared to non-exposed individuals, as suggested from mixed results from previous cross-sectional and longitudinal studies on DHEA(S) and PTSD (Gill et al., 2008; Jogems-Kosterman et al., 2007; Yehuda et al., 2006). Possibly, the assessment of DHEA instead of DHEAS levels may have shown greater predictive value, as DHEA responds more pronounced to situations of acute stress as opposed to DHEAS (Lennartsson et al., 2012).

8.2.2 Diagnostic accuracy of early PTSD risk screening (Chapter 3)

To test the diagnostic accuracy of the SPAN, TSQ and IES-R in predicting a diagnosis of PTSD at 6 months, we aimed for a fixed, high sensitivity of 80%. As previous studies in injury victims have shown sensitivities of early PTSD risk screening instruments varying between 80% to 90% (for a review, see O’Donnell et al., 2008), it may be argued that 80% sensitivity is acceptable for an early PTSD risk screener. Data of 311 of the 852 included injury patients of the AMC and VUmc hospitals were analysed who completed the instruments and clinical assessments. Eighteen patients (5.8%) of the final sample were diagnosed with PTSD at 6 months, significantly less than in excluded patients from the total sample (n = 74, 13.7%). The results showed good and similar AUCs for all instruments (0.82-0.83), indicating adequacy in distinguishing between individuals with and without PTSD at 6 months. The specificities were modest for all instruments (SPAN: 64%, TSQ: 59%, IES-R: 72%), implying poor quality in identifying non-cases. Thus, the instruments could well be used as a first selection step of possible cases, but a second, more comprehensive, diagnostic examination is needed to identify individuals in need of treatment. Importantly, the specificities did not significantly differ between tests, suggesting that the briefer instruments, SPAN and TSQ, are as accurate as the longer, IES-R.

8.2.3 The effectiveness of an internet-based early intervention to prevent PTSD (Chapters 4, 5, 6)

The main purpose of the Trauma TIPS intervention, a self-guided internet-based early psychological intervention, was to decrease acute hyperarousal and anxiety and to prevent the onset of PTSD. Learning from the experiences with psychological debriefing (Rose et al., 2003; Sijbrandij et al., 2006), the program was designed to incorporate free choice using optional features and targeted at successful recovery instead of conferring symptom information. Elements of CBT were presented in 6 consecutive steps and included information/psychoeducation, modeling, stimulating seeking social support, stress management, and in vivo exposure exercises. Pilot study results of 5 consecutive traumatic injury patients and 5 matched healthy
controls showed that the intervention was feasible and acceptable and had no immediate adverse psychological reactions for the patients or the control subjects.

To test the effectiveness of the Trauma TIPS program in preventing PTSD after injury, 300 consecutive adult injury patients from the Trauma Units of the AMC and VUmc hospitals were randomized into an intervention condition \( n = 151 \) and a control condition without intervention \( n = 149 \). PTSD symptoms decreased significantly but equally over time in both groups. In addition, there were no group differences in prevalence of PTSD and MDD diagnoses, or in severity of depression and anxiety at 12 months. Adherence to the program was low: one in five patients in the intervention group never logged into the intervention. This lack of adherence may have been the result of the freedom we allowed patients in accessing the intervention and in choosing the elements -based on the lessons learned from the debriefing studies- although similar online self-help programs suffered from comparable adherence problems (Christensen et al., 2009). Features, such as a more interactive social platform or therapist feedback, have been found to enhance participant motivation (Brouwer et al., 2011; Crutzen et al., 2011; Donkin et al., 2011), and may have increased exposure to the working elements of the program, which is needed to obtain health effects from an intervention (Crutzen et al., 2011). Another possibility is that a computerized program did not match the acute needs of the injury victims, resulting in some of them not using it. Besides limited usage of the intervention, our sample’s overall low PTSD symptom level left little room for symptom improvement for the whole group and may have led to the absence of significant group differences. Results from post hoc subgroup analyses suggested that the Trauma TIPS intervention was effective in reducing PTSD symptoms in individuals with high initial symptom levels. Based on these results, we conclude that there are currently no indications that offering a voluntary, information-based prevention program via the Internet to unselected injury victims is useful in preventing PTSD symptoms.

8.2.4
Influence of acute pharmacotherapy on PTSD development (Chapter 7)

All in-hospital administration of beta-blockers, benzodiazepines, corticosteroids and opiate analgesics within the initial 48 hrs post-injury were documented for 629 consecutive injury patients from the AMC’s Trauma Unit. Opiate administration within 48 hrs was negatively associated with 6-week PTSD symptoms, controlling for background and injury-related characteristics. Explorative univariate analyses showed that, compared to patients without any of the specified pharmacotherapy categories, fewer patients with opiate analgesics within 48 hrs post-injury were diagnosed with PTSD at 6 weeks and within the whole first year after trauma. Because beta-blockers (3.8%), corticosteroids (2.2%) and benzodiazepines (7.8%) were rarely prescribed, their role in the development of PTSD was not examined further.
In line with previous studies (Bryant et al., 2009; Holbrook et al., 2010; Nixon et al., 2010; Saxe et al., 2001; Stoddard, Jr. et al., 2009), our results points to a possible preventive effect of early opiate administration on subsequent PTSD symptom development. Our results also extend previous findings by showing that opiates may reduce the risk for PTSD, even after controlling for concurrent pharmacotherapy, and even up to 1 year post-trauma. It is possible that opiate administration early after trauma interfered with the acquisition or consolidation of fear memories, thus inhibiting the formation of intrusions of the traumatic experiences, and subsequently PTSD symptoms. Alternatively, opiates may have protected against the development of PTSD by dampening pain responses. Beta-blockers, corticosteroids and benzodiazepines were prescribed too little to examine in relation to the development of PTSD. A previous epidemiological study of adult and adolescent injury patients at a level 1 trauma center also found that these medications were rarely prescribed (Zatzick & Roy-Byrne, 2006). From our results, we conclude that our study added to the evidence of a possible beneficial effect on PTSD development of acute opiate administration after injury. However, the mechanisms that drive this effect need more clarification. Moreover, the effectiveness of in-hospital opiate analgesics compared to placebo in preventing PTSD may be tested in a randomized clinical trial in recent trauma survivors.

8.3 METHODOLOGICAL CONSIDERATIONS

8.3.1 Strengths

A particular strength of the Trauma TIPS trial is the inclusion of a large heterogeneous sample of consecutive injury patients, reflecting the broad range of injury victims presenting at a level-1 trauma centre. As opposed to studies in which participants are referred from various sources or respond to advertisements, consecutive inclusion reduces selection bias based on certain motivation from referring parties or participants themselves. We were able to include patients from two centres, which may be beneficial to the generalisability of our results. Perhaps the greatest strength of our trial were the face-to-face clinical interviews at multiple follow-up time points, allowing us to have clinical diagnoses of psychopathology besides our self-report instruments, which have been found to overestimate the prevalence of psychopathology (Fokkema, Smits, Kelder, & Cuijpers, 2013). Another strong point is the integration of the acute biological assessment into the standard procedures of the Trauma Units, which enabled the assessment of the acute stress hormone response from blood taken at the Trauma Units within minutes to hours of the traumatic event.
8.3.2

Limitations in recruitment, attrition and participation

Compared to other trauma-affected populations, such as victims of domestic violence, rape or disasters, traumatic injury patients can be identified and monitored in the immediate phase after trauma. That makes them the object of frequent investigation when it comes to the aetiology and course of post-trauma psychopathology (Koren, Arnon, & Klein, 1999; Michaels et al., 1998; O’Donnell et al., 2004; Shalev et al., 1998). However, injury survivors are not necessarily easy to motivate for (long term) research participation. Despite our repeated efforts, either in-hospital, via telephone or via postal mail, we were unable to contact one fifth \( n = 664 \) of the total adult population of the two trauma centres for participation in the trial for unknown reasons. They simply did not respond to any of our efforts. Compared to patients assessed for eligibility \( n = 1,729 \), non-responders were significantly younger \( p < .001 \) and spent less days in hospital after injury \( p < .001 \). Therefore, we cannot rule out possible selection bias of participants in the trial. Another important consideration with regard to our patient sample is the attrition at the 6 and 12 month follow-up assessments. Patients that dropped out after 6 or 12 months were more often unmarried \( p < .05 \), younger \( p < .05 \), less severely injured \( p < .01 \), had a higher GCS score \( p < .05 \) and scored higher on baseline self-reported anxiety and depressive symptoms (HADS; \( p < .01 \)) than those that remained in the study. This indicates that specific subgroups of patients might not be evenly well represented in the later assessments. Lastly, as described in Chapter 3, 330 patients of the total sample of 852 patients did not complete the screening instruments at the baseline assessment. Six month PTSD was more than twice as prevalent in patients who did not complete the screeners (14%) compared to those who did (6%), which indicates a certain reluctance for screening or research participation among patients at risk of later PTSD.

8.3.3

Statistical power

Based on previous research in comparable populations (Conlon et al., 1999), we estimated to find 19% PTSD incidence. This turned out to be 12% at 4-6 weeks post-trauma in our total sample (see Table 1.1 in the Introduction), with lower rates in subsamples, such as the RCT (Chapter 7). It may be that the psychological impact of the traumatic events leading to the injury in our study was less severe. In general, rates of psychopathology after unintentional trauma, i.e., accidents or natural disasters, are substantially lower than after intentional trauma, i.e., acts of violence, rape or war (Santiago et al., 2013). In our study this led to several
limitations. First, it may have caused lack of power to detect stronger or significant associations with acute stress hormones (Chapter 2) and acute pharmacotherapy (Chapter 7). Second, it hindered the exact determination of cut-off values for screening for a future diagnosis of PTSD, due to the limited number of participants with 6-month PTSD who completed all screening instruments (Chapter 4). Third, it may also have left little room for symptom improvement on the whole in comparing the web-based intervention and the control group (Chapter 7). In addition, it may have led participants to experience little personal incentive to access and use the intervention. Our post hoc subgroup analyses, in which we found that individuals with high initial symptom levels possibly benefited from the intervention, underscore this, although caution is necessary due to the limited size of the subgroups.

8.3.4 Generalisability

The fact that we included consecutive patients from multiple locations with heterogeneous injuries and injury mechanisms adds to the generalisability of our results to other injury populations. However, as mentioned above, one in five consecutive patients did not respond to our recruitment endeavours and thus we are uncertain whether our results are valid for this particular group. Certain patients were also excluded from participation due to restrictions in language, residency, cognitive abilities, pre-existing psychiatric morbidity or physical fitness. Therefore, caution must be met when generalizing our results to the broader population of injury patients presenting at the ER or Trauma Unit. Further, in our RCT, participants also needed to be able to log in within the first month after injury, as this was part of our design to examine the preventive effectiveness of the intervention. This inhibited us to include patients who were physically or cognitively unable to perform the intervention within our time restrictions. Lastly, translating our results to trauma-affected populations with higher conditional PTSD prevalence rates, such as survivors of violence or rape, should also be met with caution.

8.4 IMPLICATIONS FOR PRACTICE

The acute phase after traumatic injury is hectic. Perhaps before realizing the event even occurred, the survivor may be confronted with being injured, being in pain, being transported by ambulance to a hospital, undergoing extensive medical examination, and -often- being hospitalised. Not all injury patients may undergo this sequence consciously during the acute phase, but in the days and weeks that follow, they may face the impact of the event and its consequences in multiple domains of life. The injury victim may have to deal with the fear of permanent disability, with financial insecurities, with the loss of family members or even children. Unmistakably, the family of the injured victim is affected too, firstly by the shock of the incident and the injury, secondly by the effects for daily life, possibly accompanied by
personal grief. As a consequence, dealing with psychological issues may be of later importance. As our and previous studies have shown, most patients are resilient and show a natural psychological recovery within the first year. A proportion of trauma patients, however, develop persistent psychological symptoms, and those are the patients worth targeting early on.

The results from our RCT suggest that patients with high initial PTSD symptoms may benefit from an early psychological internet intervention, such as the Trauma TIPS program. Due to power issues we do not know whether the intervention may have also worked for patients with lower levels of acute distress. However, the Trauma TIPS program showed potential in preventing PTSD, as one of the few universal self-help psychological interventions targeting a recently traumatized sample. Important aspects in the clinical implication for trauma patients are its voluntary nature, allowing patients to match elements of the program to their needs in their own timeframe, and the low burden on existing personnel resources. Certain modifications to the program may increase its effectiveness. Using mobile application software increases flexibility for usage of the program, especially for bedridden patients with limited access to computers or laptops. In addition, mobile applications can be linked to alert messages, social platforms and information services that may also positively affect adherence to the program, as previous studies have shown (Kelders, Kok, Ossebaard, & Van Gemert-Pijnen, 2012). Another modification is allowing the possibility for guided self-help. A recent RCT showed that offering imaginal and in vivo exposure as early as 24 hrs after injury, and followed up at one and two weeks later, may prevent the development of PTSD symptoms (Rothbaum et al., 2012). Besides offering information on in vivo self-exposure exercises, as currently in the program, a module may be added that allows patients to design their personal in vivo exposure hierarchy in consultation with a therapist. A similar guided self-help protocol has shown promise in the treatment of PTSD patients (Rothbaum et al., 2012). This may also include follow-up monitoring and feedback, and could involve the patient’s social network, both for support to the patient and for the wellbeing of the family members themselves.

Within a stepped care approach for trauma survivors, this program may fit as an intermediate step before offering curative treatment for PTSD, such as CBT or EMDR. Ideally, the program is offered to survivors with high initial distress. This implies that injury patients are screened systematically to select those with the worst prognosis for psychological recovery. Screening for early PTSD symptom levels in the days following injury has shown predictive for chronic PTSD. Therefore, one possibility to implement early screening after injury is to register email addresses or mobile telephone numbers at the ER or Trauma Unit to contact patients in the subsequent days or weeks for voluntary screening and monitoring of symptoms. This may also be done via email or mobile applications alerts, and may be linked to information services for follow-up contact with a personal GP or trauma specialist. The screening questionnaire may consist of the SPAN, TSQ, or IES-R, as these showed comparable results in prognostic accuracy for 6 month PTSD. In practice,
when patients score high on acute distress, they may be offered the Trauma TIPS program as a next step together with monitoring of the symptom course. If symptoms persist, patients are to be followed up with more elaborate diagnostic examination and treatment if necessary.

Although acute cortisol levels contributed significantly to the development of PTSD, its use as an individual biological screener for PTSD, especially considering the low explained variance found in our sample, still has to be proven. Our results confirmed the assumption that HPA-axis dysregulations may impair the possibility for recovery after trauma (Yehuda, 2002). Consequently, this solidifies the basis for interventions on the acute glucocorticoid response, congruent with results from recent studies (Delahanty et al., 2013; Schelling et al., 1999; Schelling et al., 2001; Schelling et al., 2004; Schelling et al., 2006; Zohar, Yahalom et al., 2011).

Our observed association between early opiate administration and fewer PTSD symptoms at 6 weeks may indicate that morphine benefits psychological recovery after injury. However, the nature of the study precludes inferences about causality and effectiveness. An additional consequence of early morphine administration may also be impairment of declarative memory. Besides impairment of fear conditioning (Szczytkowski-Thomson et al., 2013) and of newly retrieved memory under conditions of intense stress (Schneider et al., 2013), morphine may also impair the consolidation of details of the event that may be useful to recollect for other purposes, such as in criminal law cases. Therefore, more knowledge into opiate’s effects on memory is needed.

### 8.5 Future Research

Based on the results from our study, we propose several suggestions for future research. First, the Trauma TIPS intervention may be modified to mobile applications with more adherence increasing features, as described above, possibly adding therapist guidance in performing in vivo exposure exercises, and subsequently tested for feasibility before implementing in injury populations. This may include user-based evaluations of the elements in the program, to ensure that the program elements are functional, but also easy to understand and perform (Kassam-Adams, 2014). Additionally, the effectiveness of the Trauma TIPS intervention in individuals with high levels of distress needs to be replicated in a randomized controlled trial.

As mentioned in the previous paragraph, the sensitivity and specificity of acute cortisol for predicting future PTSD needs to be examined to make inferences on its usefulness as an early PTSD risk screener. Acute cortisol levels have shown an interesting biomarker for augmenting the acute stress response (Zohar, Yahalom et al., 2011; Zohar, Juven-Wetzler et al., 2011). As an addition to current studies, it would be interesting to examine whether administering hydrocortisone to acutely injured trauma patients may increase the effects of preventive exposure exercises, as previous studies have shown that hydrocortisone increases extinction learning (de Quervain et al., 2011).
Another suggestion for future research is to investigate the effectiveness of early opiate analgesics on preventing PTSD after injury in a RCT, as the current findings of our and previous studies have been limited to observed associations in injury samples (Bryant et al., 2009; Holbrook et al., 2010; Nixon et al., 2010; Saxe et al., 2001; Stoddard, Jr. et al., 2009).

In terms of a stepped care approach for PTSD after injury, future research may examine the effectiveness of early screening, monitoring, offering of a (guided) self-help program and curative treatment compared to care as usual. At this instance, care as usual implies that patients have intensive medical contact during their time in the ER and hospital stay, but are out of sight when they leave the hospital. Some may have a follow-up appointment at the trauma specialist or GP for their injuries, but generally no check-up of psychological wellbeing at any stage during this time. Early referral to psychological services of patients with high initial distress is incidental and dependent on the mindfulness of the trauma staff member or GP. To date, no comprehensive study of the effectiveness of stepped care for PTSD after injury has been performed.